PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference M30317PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/07744	International filing date *(day/month/year)* 16.07.2003	Priority date *(day/month/year)* 16.07.2002
International Patent Classification (IPC) or both national classification and IPC C12N9/02		
Applicant MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MED..., et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.12.2003	12.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Sommer, B Telephone No. +49 89 2399-7099

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07744

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-30 as originally filed

Claims, Numbers

1-28 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12-17, 23, 24, 28

   because:

   ☒ the said international application, or the said claims Nos. 12-17, 23, 24, 28 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-12, 15-18 and 20-28 (all completely); 13 and 14 (all partially) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3, 10, 11, 17, 18, 20, 21, 24-28
	No:	Claims	1, 2, 4-9, 12-16, 22, 23
Inventive step (IS)	Yes:	Claims	3, 10, 11, 17, 18, 20, 21, 24-28
	No:	Claims	1, 2, 4-9, 12-16, 22, 23
Industrial applicability (IA)	Yes:	Claims	3, 10, 11, 18, 20, 21, 25-27
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item II

The current assessment is based on the assumption that all claims enjoy the priority rights from the filing date of the priority document (16.07.2002), i.e. the documents mentioned in the International Search Report (ISR) as P-documents are not taken into account.

Re Item IV

The IPEA agrees with the objection put forward in the ISR as to lack of unity and considers that the groups of inventions mentioned in the ISR are not so linked as to form a single general inventive concept (**Rule 13 PCT**). Since the applicant has not had a search report drawn upon all inventions, the preliminary examination was prosecuted on the basis of the inventions in respect of which a search has been carried out, i.e. on the first group of inventions relating to an isolated nucleic acid sequence which encodes for a polypeptide with neuronal tryptophan hydroxylase activity as well as subject-matter related thereto. For the purpose of the preliminary examination, the inventive concept common to all three subinventions of said group is considered as species homologues of a TPH isoform based on sequence identities of more than 90%. During substantive examination in the regional phase, said concept may turn out to be not novel, dependent on the validity of the priority documents and thus any of the species homologues might then have to be considered as a separate invention. Finally, the present set of claims is still not unitary, since the applicant did not restrict the claims to the above mentioned group of inventions.

Re Item V

1. Reference is made to the following documents (D):

   D1: WO 02/17891 A

2. The present invention discloses an isoform of tryptophan hydroxylase (TPH2; snTPH) of human origin (SEQ ID Nos.1 and 2) as well as species homologues thereof from mouse and rat (SEQ ID Nos. 3-6). Said TPH2 is expressed in the CNS and used for the modulation of serotonin biosynthesis and the treatment of neuronal diseases.

3. D1 discloses a neuron-specific isoform of TPH detected in mouse brain sharing 59% identity with SEQ ID No. 4 of the present application in a 488 aa overlap. Moreover, methods of modulating the serotonin biosynthesis are disclosed, e.g. using ribozymes, antisense molecules, specific TPH inhibitors or overexpression (D1, e.g. claims). The nucleic acid and/or gene of D1 encoding said neuron specific TPH isoform (e.g. D1, figure 5-7) can be interpreted as a "recombinant nucleic acid molecule containing ... [undefined] parts of the nucleic acid sequence [according to claim 1]...". Consequently,

claims 4-7, 12-16 and 23 of the present application are not novel in view of D1.

According to the description, page 22, lines 12-13, "... the derived amino acid sequence of this enzyme [the neuronal TPH from mouse] shows a homology of 86% in relation to the classical [known] mouse TPH sequence...". Therefore, claim 1c) as well as claims 2 and 4-9, insofar as they refer to claim 1(c), cannot be considered as being novel.

Claim 1d) refers to "a human genomic nucleic acid sequence, which contains the gene for sn-TPH and exhibits polymorphisms". Both said nucleic acid sequence as well as said gene are undefined. Therefore, a DNA preparation of the complete human genome anticipates the novelty of claim 1d), since such a preparation contains the [undefined] gene for sn-TPH and exhibits polymorphisms. As a result, any polypeptide encoded by the human genome is novelty-destroying for claim 2, insofar as it refers to claim 1d). Moreover, any recombinant nucleic acid molecule connected with at least one regulatory signal can be interpreted in the sense of claim 4 as "... containing ... [undefined] parts of the nucleic acid sequence [according to claim 1]...", since already one single amino acid is considered as a "part of a sequence according to claim 1" and no functional requirements are mentioned for said "parts".
Therefore, the subject-matter of claims 1, 2, 4-7, 22 and 23 is not novel.

In summary, none of claims 1, 2, 4-9, 12-16, 22 and 23 meets the requirements of **Article 33(2) PCT**.

4. D1, which discloses the existence of at least one neuron-specific TPH isoform in mouse brain, is considered as most relevant prior art to assess the inventive step of the present invention. The TPH isoform of the present application differs from D1 in its primary sequence. The problem to be solved is formulated as the provision of a further TPH isoform. The solution provided by the application is human neuron-specific TPH2 as well as its murine and rat homologues.

The prior art provides strong evidence for the existence of more than one TPH isoform in brain and discloses the production of antisera directed against said presumably splicing isoforms (e.g. D1, figure 7 or D3, abstract; page 570, left-hand column, second paragraph). However, the prior art neither teaches nor suggests the existence of a further neuron-specific TPH derived form a different chromosomal locus, which is highly homologous to known TPHs at the amino acid level but shows only little similarity with the known TPH genes at the nucleic acid level (description, page 3, last paragraph).

Consequently, claims 3, 10, 11, 17, 18, 20, 21 and 24-28 are considered as involving an inventive step (**Article 33(3) PCT**).

5. Claims 12-17, 23, 24 and 28 relate to subject-matter considered by this Authority to be covered by the provisions of **Rule 67.1(iv) PCT**. No opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (**Article 34(4)(a)(I) PCT**). For the assessment of the present claim 12-17, 23, 24 and 28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6. Claim 11 relates to a compound only defined by reference to its isolation method. The claim covers all compounds which are isolated by the method of claim 10, whereas the application provides support within the meaning of **Article 5 PCT** for only one of said compounds. The only example for such a compound disclosed in the application are TPH antibodies. The nature of other compounds identified by the method of claim 10 is completely unclear. The claim also lacks clarity (**Article 6 PCT**) since an attempt is made to define the compound by reference to a result to be achieved.

7. The term "snTPH" used in claims 1, 10, 12, 13, 15, 18 and 24 lacks clarity. As it does not represent a commonly used abbreviation with a well-recognised meaning, the subject-matter is only defined by an arbitrary designation, which renders the scope of said claims unclear. A protein, DNA or gene has to be regarded as a chemical compound which must be clearly characterized by reference to technical features e.g. by ist sequence or as a product by process in order to satisfy the requirements of **Article 6 PCT**, but not merely by ist function or by a result to be achieved.

8. Each of the amino acid sequences listed in the description for the human, mouse and rat nTPH (description, pages 27-30) differs in at least three amino acids from SEQ ID Nos. 2, 4 and 6, respectively, of the sequence listing, thereby rendering the application unclear (**Article 6 PCT**). Each of the amino acid sequences in the description is three amino acids shorter that the sequences in the sequence listing.